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ORIGINAL REPORT

Comparison of various measures for assessing medication refill adherence using prescription data†

N. M. Vink MD[1], O. H. Klungel PharmD PhD[2], R. P. Stolk MD, PhD[1,3] and P. Denig PhD[3,4]*

[1]*Department of Epidemiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[2]*Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht University for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands*
[3]*Share Graduate School for Health Research, Groningen, The Netherlands*
[4]*Clinical Pharmacology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands*

SUMMARY

Background Several measures using prescription data have been developed for estimating medication refill adherence. Few studies have made direct comparisons, and little is known about the accuracy of these measures in patients on a multiple-drug regimen.
Purpose To compare different calculation methods using prescription data for assessing refill adherence.
Method An observational cohort study among type 2 diabetes patients was conducted. Adherence to oral glucose-lowering, antihypertensive and lipid-lowering medication was assessed for 2004. We calculated medication possession ratios in a flexible period (MPRF), per calendar year (MPRY) and gaps between refills (GAP) at drug class and therapeutic level. Individual review of drug prescription profiles was conducted to validate identified cases of suboptimal refill adherence. Differences in Area Under the Curve (AUC) of ROC-curves were calculated to compare the methods.
Results Of the 3877 patients, 2969 (77%) patients received oral glucose-lowering medication, 2715 (70%) antihypertensives and 1797 (46%) lipid-lowering medication. Using cutoffs for MPR $< 80\%$ and GAP > 30 days, overall rates of suboptimal adherence for these drug classes were 32, 35 and 23% respectively. AUC for measures calculated at drug class level (range 0.85–0.90) were significantly larger than those calculated at therapeutic level (0.72–0.90). For oral glucose-regulating medication and antihypertensives, AUCs were largest for the MPRY and GAP measures (0.87–0.88). For lipid-lowering medication, the AUC was largest for the GAP measure (0.90).
Conclusions Differences between adherence measures were small and favoured calculation on drug class level. For multiple drug use, both MPRY and GAP were good measures for identifying suboptimal refill adherence. Copyright © 2008 John Wiley & Sons, Ltd.

KEY WORDS — patient compliance; diabetes mellitus type 2; administrative data; primary health care; drug utilization

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INTRODUCTION

Suboptimal medication adherence is a common problem in clinical practice.[1,2] Especially in patients in need of various chronic preventive drugs, problems with discontinuation and under use of medication may lead to suboptimal achievement of therapeutic targets.[1,3,4] Automated databases with prescription refill data are increasingly being used for identifying patients with possible medication adherence problems.[5–7]

For estimating medication refill adherence, different methods have been proposed, some focusing on the duration or continuation of drug refills—often called persistence—and others more on the sufficient amount or timely refill of medication within a period of persistence.[7,8] The most simple approach is the anniversary model.[8] Patient adherence to medication is based on refilling one prescription at the end of the study period. This approach may be adequate for measuring persistence but fully disregards the amount of drugs being refilled during the study period.[8] In the minimum-refills model, a patient is considered adherent with treatment when a specified number of prescriptions is refilled during the study period.[7,8] This is still a very rough estimate of the drug amount being

* Correspondence to: Dr P. Denig, University Medical Centre Groningen, Sector F, Department of Clinical Pharmacology, PO Box 196, 9700 AD, Groningen, The Netherlands. E-mail: P. Denig@med.umcg.nl
† The authors declare that they have no conflict of interest regarding this work.

refilled. A better estimate can be achieved by calculating the medication possession ratio (MPR).[5–9] This is based on the proportion (or percentage) of days' supply obtained during a specific time period or over a period of refill intervals. This method, however, disregards the timeliness of refilling.[6,8] To take timely refilling into account, methods based on refill sequence are needed.[6] Using the start and expected end dates of prescriptions, the medication gaps between refills (GAP) can be calculated.

There is no consensus about the best approach for determining refill adherence using prescription data.[5,6,8–10] Different methods may provide complementary information on refill patterns.[9,11] It has been advocated that one should at least try to assess adherence in terms of persistence and adequate extent of refills.[8] So far, little attention has been paid to calculating refill adherence in patients using multiple drug regimes. Usually, refill adherence is calculated for individual drugs and sometimes averaged over the different drugs used by one patient. When adherence is calculated on individual drug level, no consideration is given to patients who switch their medication during the study period. When adherence is calculated on drug class level (e.g. β-blocking agents) or on therapeutic level (e.g. antihypertensive medication) switches between drugs from the same class or for the same indication are taken into account. Studies on persistence using refill-sequence models often permit switches between drugs with shared indications.[8]

The main aim of this study was to identify preferred measures for assessing suboptimal medication refill adherence using prescription data. The outcomes of all measures were tested against a reference method based on individual, visual review of the prescription refill patterns. Next, we made the following comparisons: (1) between different measures based on MPR and based on GAP, (2) between calculations made on drug class and on therapeutic level.

METHODS

We conducted an observational cohort study in all 3877 patients diagnosed and managed for type 2 diabetes mellitus on 1 January 2005 by 38 general practitioners (GPs) participating in the GIANTT (Groningen Initiative to ANalyse Type 2 diabetes Treatment) project.[12] These GPs practiced in one region in The Netherlands. Since all GPs prescribed electronically, full prescription information is recorded in the electronic medical records. Patients that had left the practice before 1-January 2005, and therefore would have incomplete data, were excluded.

Data collection

The following routinely recorded data were extracted from the GPs' electronic medical records: age, gender, date of diagnosis of diabetes mellitus type 2, blood pressure and laboratory measurements, and all prescriptions for glucose-lowering medication, antihypertensive medication and lipid-lowering medication, including prescribed daily doses and total quantities prescribed. The study was conducted in conformance to the Dutch guidelines on the use of medical data for scientific research. For medical record research of anonymous data, no IRB approval is needed in The Netherlands.

Measures of refill adherence

The study was set up to compare different commonly used approaches for calculating medication refill adherence in patients that may use multiple drugs or switch between drugs. Refill adherence was assessed for the year 2004. It was calculated for three types of medications: oral glucose-lowering medication, antihypertensive medication and lipid-lowering medication. Included were two MPR measures that assess the maximum proportion of days a patient could have taken the medication as prescribed, and the GAP measure that assesses whether a patient refilled the medication in time. Both MPR and GAP measures are used to identify patients that show suboptimal medication refill adherence using some (arbitrary) cutoff to divide patients as being adherent or non-adherent.[6,7] The underlying assumption is that a patient is either under-using or stopped using the medication when he/she does not refill medication as expected. Oversupply is truncated at 100%, since these measures do not address overuse of medication. In case of overlapping prescriptions, the second prescription is shifted forward (see Figure 1), clustering prescriptions at drugs class or therapeutic level (see next section). This provides a conservative estimate of suboptimal adherence, since it accepts that the medication may be taken sequentially.

The measures were defined as follows (see also Figure 1):

- Medication possession ratio using a flexible period (MPRF), i.e. the number of days for which prescribed medication was available between the last refill in the observation year and the last refill in the preceding year (or the first refill in the observation year when there were no prescriptions in the preceding year) divided by number of days between these refills, expressed as percentage. By definition, this method does not include terminal gaps and

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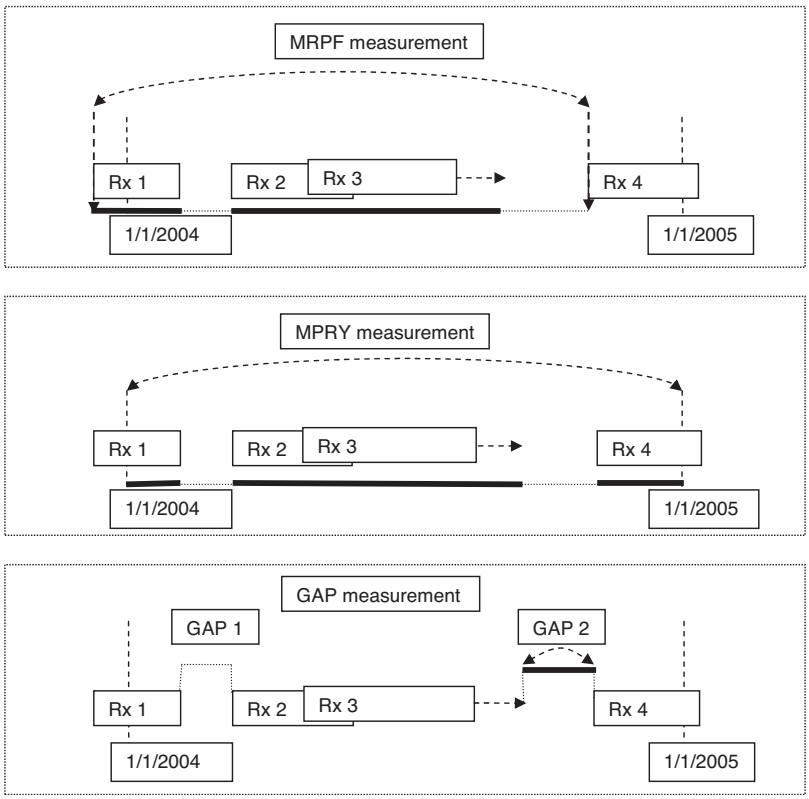

Figure 1. Examples of MPRF, MPRY and GAP (largest gap between refills) measurements; Rx are prescriptions. After adjusting for overlapping prescriptions, the bold black lines for the MPRF/MPRY show the days for which prescribed medication was available, whereas the bold black line for the GAP shows the largest gap

thus disregards persistence. Assessment of adherence over short time intervals is likely to be imprecise and could bias the MPR upwards[5,6]. Patients for whom the period between the first and last refill was less than 90 days, are therefore assessed as adherent according to this measure. The percentage of patients for whom this occurred was 5% for oral glucose-lowering medication, 3% for antihypertensive medication and 18% for lipid-lowering medication.

- Medication possession ratio using a fixed 1-year period (MPRY), i.e. the numbers of days for which prescribed medication was available during the observation year 2004 divided by 366 days, for patients already receiving drugs in the preceding year. This method assesses persistence in addition to adequate extent of refills but—by definition—does not address refill adherence of initial users during the observation year. The percentage of such patients receiving an initial prescription during the observation year was 18% for oral glucose-lowering medication, 11% for antihypertensive medication and 34% for lipid-lowering medication.
- GAP, i.e. the number of days between the calculated end date of a prescription and the start date of the following prescription. By identifying the largest gap, this method assesses the maximum single-interval period for which there was an insufficient refill of medication. To calculate the adherence rate, the gap is divided by 366 days, expressed as percentage, and then subtracted from 100%.

When information about the daily doses or the total medication quantities were missing, refill adherence percentages cannot be calculated, and patients were excluded from the analysis. Percentage of patients with such incomplete information ranged between 2 and 5%, and were similar for all tested measures.

Drug class and therapeutic level

Medication was classified according to the ATC-system (Anatomical Therapeutic Chemical Classification system). All measures were first calculated on drug class level, i.e. for oral glucose-lowering medication this includes biguanides (ATC-codes A10BA + A10BD), SU-derivates (A10BB + A10BD02), acarbose (A10BF), glitazones (A10BG + A10BD03) and glinides (A10BX). For antihypertensives, these are the diuretics (C03 + C07B + C07C + C07D + C08G + C09BA + C09DA), beta-blocking agents (C07),

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calcium-antagonists (C08 + C09BB) and RAS-inhibitors (C09). For lipid-lowering medication, these are statins (C10AA), fibrates (C10AB), bile acid sequestrans (C10AC), nicotinic acid derivates (C10AD) and other lipid modifying drugs (C10AX). Furthermore, we calculated the MPRY and GAP at the higher therapeutic class level, i.e. glucose-lowering medication (A10B), antihypertensives (C03 + C07 + C08 + C09) and lipid-lowering medication (C10).

The calculation on drug class level accounts for switches and overlapping refills within these drug classes, whereas calculation on therapeutic levels also takes switches between drug classes and overlapping refills at therapeutic level into account.

Reference method

Individual review of refill patterns was used as reference method to validate the outcomes of the different measures of calculating medication refill adherence. All patients with a MPRF or MPRY of less than 100%, or a GAP greater than 7 days were reviewed. For each patient, graphs were generated showing all prescriptions with the periods covered by each prescription as well as the related measurements of clinical outcomes, i.e. glycemic, blood pressure and lipid measurements. These patient profiles were visually assessed through a step-wise procedure to eliminate possible misclassifications that were not considered to represent suboptimal refill adherence, using a 'grace' period of 7 days after the correction for overlapping refills. Based on a pilot study where three researchers assessed between 400 and 500 refill patterns for each of the three therapeutic groups, and recommendations made by the Dutch Institute for Rational Drug Use,[13] the following criteria for misclassifications were included:

1. single prescriptions of 14 days or less for diuretics and beta-blocking medication. These were not considered to represent suboptimal refill adherence, since short-term prescribing of these drugs may occur for alternative, non-chronic indications;
2. errors in the recorded dosing scheme, e.g. prescriptions with a total quantity of 0 or 1, or a gap that can be compensated by oversupply from the last refill preceding the measurement calculation;
3. switches between drugs for the same therapeutic class within 7 days. These were defined as adequate refill adherence;
4. concurrent gaps in all prescriptions and risk factor measurements, indication of a period of incomplete documentation in the electronic medical record, for instance due to a hospital admission;
5. gaps observed in oral glucose regulating medication in the period shortly after a start with insulin.

Analysis

We did not use fixed cutoffs to define medication refill adherence but for the descriptive analysis of adherence rates we used both very strict cutoffs (MPR < 100% and GAP > 7days) as well as commonly used cutoffs (MPR < 80% and GAP > 30 days). Adherence rates were calculated after exclusion of misclassifications, resulting in so-called validated (overall) adherence rates. For each measure and drug level, the sensitivity and specificity were calculated in comparison to the individual review outcomes. ROC curves were drawn and Area Under the Curve (AUC) were calculated for the whole range of cutoffs. To compare and test for differences in the performance of different measures, differences of AUC (with 95% confidence interval) were calculated, using the method of Hanley *et al.*[14] This method compares AUC derived from the same set of patients by taking into account the correlation between the areas. We considered AUCs between 0.8 and 0.9 as indicating good performance, and higher than 0.9 as indicating excellent performance.

RESULTS

The mean age of all patients was 66 years, and 46% were male (Table 1). Of all patients, 2969 (77%) received oral glucose-lowering medication, 2715 (70%) received antihypertensive medication and 1797 (46%) received lipid-lowering medication in 2004 (Table 1).

Individual review of the refill adherence patterns at drug class level resulted in 11% misclassifications, being cases with a calculated incomplete refill of more than 7 days but fulfilling one of the predefined criteria for misclassification. After correction for misclassifications, suboptimal refill adherence was calculated for various cutoffs used for defining patients' adherence.

Table 1. Characteristics of study cohort

Number of patients	3877
Male sex	45.6%
Age, mean (SD)	66.1 year (12.6)
Diabetes duration, median (IQR)	3.0 (1.0–7.0)
HbA1c, mean (SD)	7.2% (1.2)
Systolic blood pressure, mean (SD)	147 mmHg (18)
Total cholesterol, mean (SD)	5.1 mmol/l (1.0)
Insulin	15%
Oral glucose-lowering medication	77%
Antihypertensive medication	70%
Lipid-lowering medication	46%

HbA1c = Glycosylated hemoglobin; SD = standard deviation; IQR = interquartile range.

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Table 2. Suboptimal refill adherence rates according to the various measures

Measure and cutoff used	Number of patients receiving the following medication		
	Glucose-lowering $N = 2756$ Non-adherent	Antihypertensive $N = 2502$ Non-adherent	Lipid-lowering $N = 1713$ Non-adherent
MPRF drug class <80%	462 (17%)	485 (19%)	218 (13%)
MPRY drug class <80%	608 (22%)	556 (22%)	222 (13%)
GAP drug class >30 days	620 (23%)	643 (26%)	305 (18%)
MPRY therapeutic level <80%	383 (14%)	261 (10%)	216 (13%)
GAP therapeutic level >30 days	457 (17%)	339 (14%)	299 (18%)
Validated overall rate	878 (32%)	874 (35%)	387 (23%)

MPRF = medication possession ratio calculated using a flexible period; MPRY = medication possession ratio calculated using 1 year; GAP = (largest) gap between refills.

Using the strict criteria of the MPR <100% and the GAP >7 days, overall suboptimal adherence rates as validated by the reference method were 58% (1600 patients) for oral glucose-lowering medication, 61% (1534 patients) for antihypertensive patients and 49% (832 patients) for lipid-lowering medication. When using the cutoffs most frequently used in the literature (MPR <80% and GAP >30 days), the overall rates validated by the reference method were 32, 35 and 23%, respectively (Table 2).

The ROC curves for all measures at drug class level showed steep increases, with sensitivities between 60 and 70% at specificities between 95 and 80% for identifying suboptimal refill adherence as validated by the reference method (Table 3). For oral glucose-lowering and antihypertensive medication, the sensitivities were higher for the MPRY and GAP in comparison to MPRF measure, whereas for lipid-lowering medication especially the GAP measure showed higher sensitivities over a range of cutoffs. For measures calculated at therapeutic level, the sensitivities were clearly lower in comparison to the drug class level for both oral glucose-lowering and antihypertensive medication (Table 3).

AUC for measures calculated at drug class level (range 0.85–0.90) were significantly larger than those calculated at therapeutic level (0.72–0.90) (Table 4). For oral glucose-regulating medication and antihypertensives, AUCs above 0.8 were observed for the MPRY and GAP measures (0.87–0.88). For lipid-lowering medication, the AUC was largest for the GAP measure (0.90) but high AUCs were also observed for the MPRF and MPRY measures (0.86). Comparing the AUC for identifying suboptimal refill adherence as validated by the reference method, the MPRY and GAP measures were significantly better than the MPRF for oral glucose-lowering and antihypertensive medication (Table 4). For lipid-lowering medication, the GAP

Table 3. Sensitivity and specificity of the various measures for identifying refill adherence

	Number of patients receiving the following medication					
	glucose-lowering ($N = 2756$)		Antihypertensive ($N = 2502$)		Lipid-lowering ($N = 1713$)	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
MPRF drug class <70%	17.8%	99.6%	22.5%	99.2%	16.0%	99.7%
MPRF drug class <80%	28.9%	99.2%	31.6%	99.1%	26.2%	99.3%
MPRF drug class <90%	44.8%	98.3%	48.3%	97.7%	44.5%	98.8%
MPRF drug class <95%	61.6%	95.3%	63.6%	94.6%	60.8%	96.5%
MPRY drug class <70%	27.1%	97.7%	25.6%	96.7%	15.7%	99.9%
MPRY drug class <80%	38.0%	97.1%	36.2%	96.5%	26.7%	99.4%
MPRY drug class <90%	56.4%	95.6%	55.9%	94.0%	45.8%	98.8%
MPRY drug class <95%	74.4%	91.5%	74.6%	89.0%	66.2%	94.8%
GAP drug class >7 days	82.4%	86.2%	84.2%	82.7%	85.3%	90.4%
GAP drug class >15 days	60.6%	94.3%	63.2%	92.8%	60.3%	95.2%
GAP drug class >30 days	38.8%	97.9%	41.9%	97.6%	36.6%	98.6%
MPRY therapeutic level <70%	15.8%	99.7%	11.3%	99.5%	15.0%	99.9%
MPRY therapeutic level <80%	23.9%	99.3%	17.0%	99.4%	26.0%	99.4%
MPRY therapeutic level <90%	38.4%	97.8%	30.2%	97.6%	44.8%	98.8%
MPRY therapeutic level <95%	53.5%	95.2%	44.0%	94.4%	64.9%	94.8%
GAP therapeutic level >7 days	62.8%	88.3%	55.5%	87.4%	83.8%	90.5%
GAP therapeutic level >15 days	43.2%	95.2%	37.6%	94.9%	59.3%	95.2%
GAP therapeutic level >30 days	27.2%	98.0%	22.1%	97.8%	35.9%	98.6%

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Table 4. Comparison of the various measures to the reference method: AUC of ROC curves with standard errors (SE)

Measure and level used	AUC (SE) glucose-lowering medication	AUC (SE) antihypertensive medication	AUC (SE) lipid-lowering medication
MPRF on drug class level	0.847 (0.007)	0.857 (0.008)	0.861 (0.010)
MPRY on drug class level	**0.883**[*†] (0.007)	**0.868**[*†] (0.008)	0.858 (0.010)
GAP on drug class level	**0.873**[*†] (0.007)	**0.874**[*†] (0.007)	**0.904**[‡§] (0.008)
MPRY on therapeutic level	0.800[‖] (0.008)	0.727[‖] (0.010)	0.850 (0.010)
GAP on therapeutic level	0.775 (0.009)	0.717 (0.010)	0.895[¶] (0.008)

MPRF = medication possession ratio calculated using a flexible period; MPRY = medication possession ratio calculated using 1 year; GAP = (largest) gap between refills; in bold are the largest AUCs for each therapeutic area are given.
[*]AUC for MPRY/GAP significantly higher in comparison to MPRF on drug class level.
[†]AUC for MRPY/GAP on drug class level significantly higher in comparison to therapeutic level.
[‡]AUC for GAP significantly higher in comparison to MPRF/MPRY on drug class level.
[§]AUC for GAP on drug class level significantly higher in comparison to therapeutic level.
[‖]AUC for MPRY significantly higher in comparison to GAP on therapeutic level.
[¶]AUC for GAP significantly higher in comparison to MPRY on therapeutic level.

method was significantly better than the measures based on MPR. Measures calculated on drug class level were significantly better for all three medication groups in comparison with measures calculated on therapeutic level (Table 4).

DISCUSSION

We found that for therapeutic areas where multiple drug use is common, both the MPRY and calculation of GAP are suitable measures to identify suboptimal medication refill adherence. For assessing suboptimal refill adherence in an area where single drug use is common, GAP appears to be the most sensitive method. Furthermore, we observed that measures calculated on drug class level were significantly better than measures calculated on therapeutic level.

Previous investigations assessing medication adherence with prescription refill data did not lead to consensus about the best measure. Adherence has been defined ambiguously in the literature, which makes it difficult to draw conclusions about the best measure to use. Hess *et al*. concluded that the medication refill adherence measure, in our study called the MPR, is the preferred method, because of its simplicity and the fact that it provides results identical to those achieved with other continuous measures of medication possession or GAP.[9] Caeteno *et al*. concluded that the best measure for assessing adherence problems was the use of a hybrid model, combining continuation and sufficient amount of refills of medication.[8] Our findings support these conclusions, especially in multiple drug users, since our MPRY measure addressed both aspects of adherence and showed good performance (high AUCs) for identifying suboptimal refill adherence despite the fact that it focused only on prevalent users. The sensitivity could be further improved by calculating the MPRY also for initial users starting at the time of their first prescription. In that case, either the follow-up period must be extended to include a 1 year period or a shorter follow-up period should be accepted. The specificity could be improved by including the criteria used in our visual assessment. However, this requires a more complicated algorithm and additional data.

Previously, not much attention has been given to the issue of calculating adherence in patients using multiple drugs for the same indication. We tested whether calculating adherence percentages on therapeutic level might provide better results than at drug class level, as it takes switching between drug classes into account. In our study, the numbers of patients misclassified due to switches between drugs, however, was much smaller than the number of cases missed when looking at the aggregated therapeutic level. Therefore, we conclude that assessments on therapeutic level were not sufficiently comprehensive in this case.

Several limitations of this study should be recognized. First, when using prescription refill data one does not measure true adherence behaviour, since not all prescribed medication will be actually taken by the patients. This is a widely known problem using prescription refill data, and results in an overestimation of actual adherence for all tested measures. In particular, we used prescription and not dispensing data, which are more susceptible to overestimation. Furthermore, the reference method assessment was performed visually by a single investigator. To avoid misclassification bias, however, a strict stepwise procedure was used with explicit assessment criteria.

Conclusions and recommendations

Differences between adherence measures were small and favoured calculation on drug class level. For

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KEY POINTS

- Both the MPR and GAP are good measures for identifying medication refill adherence in patients using multiple drugs.
- Calculation of medication refill adherence on drug class level is better than on indication level to deal with possible switches among drugs.

multiple drug use, both MPRY and GAP were good measures for identifying suboptimal medication refill adherence. MPRY is a simple measure, which could be improved by including patient receiving an initial refill during the study period. Because of the simplicity of calculation, we recommend the MPRY for assessing refill adherence in patients on a multiple drug regimen.

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